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Organocatalytic ring-opening polymerization of *L*-lactide in bulk: A long standing challenge.

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ABSTRACT

The exponential increase in the use of plastic demands that biosourced and biodegradable polymers such as poly(*L*-lactide)s (PLLA)s be considered to replace some petroleum based polymers in a range of applications. In order to produce PLLA in the greenest manner, *i.e.* by ring-opening polymerization (ROP) of *L*-lactide using an organocatalyst in solvent free conditions at high temperature (in bulk) has proven to be a significant challenge. Indeed, the high required temperature (180 °C) has led to poorly controlled polymerizations as a result of transesterification reactions of the PLLA backbone, racemization of the lactide monomers as well as the degradation and thus deactivation of the organocatalyst. We report herein the efforts made over the past 20 years in order to conduct the ROP of *L*-lactide in bulk by using organic molecules and the problems encountered by the scientific community in addressing this challenge to date.

INTRODUCTION

As a consequence of the increased demand for plastics that results from their low cost, light weight nature, versatility and durability, production has exponentially grown from 1964 reaching 311 million tons in 2014 and is expected to double again in 20 years [1].This industry provides a tremendous utility in our daily lives, however, it has a frightful impact on our environment. Between 4.8 and 12.7 million metric tons of plastic entered in the ocean in 2010 [2], *i.e.* between one and four hundred kilograms of plastic enter our oceans each second. In order to reduce plastic waste, recycling and energy recovery have been

implemented to a limited extent however these efforts are insufficient to deal with the ever increasing volumes of plastic that our society uses. In this respect polylactides (PLA)s, which are derived from biomass sources, are of special interest as a consequence of their biocompatiblity and, more importantly in this regard, biodegradability [3].

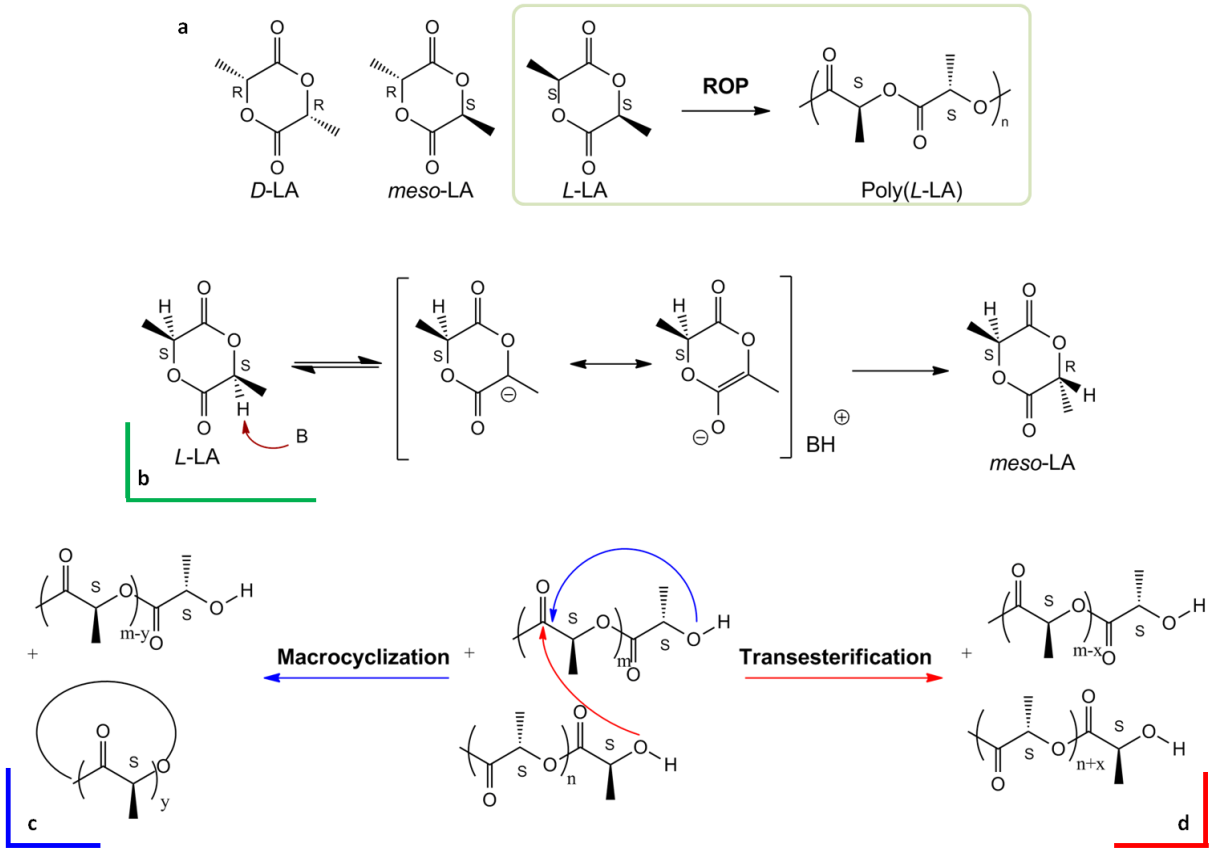

Figure 1. Different isomers of lactide and the poly(*L*-lactide) structure (a). Possible side reactions during the ROP of LLA in bulk: (b) Base-catalyzed racemization of LLA *via* reversible deprotonation of the α-CH group with intermediate formation of a planar delocalized anion (B = Base), (c) Macrocyclization by intramolecular backbiting and (d) transesterification reactions by intermolecular backbiting.

PLAs are typically synthesized by ring-opening polymerization (ROP) of a lactide (LA), cyclic diester monomer (Figure 1a) and have a range of properties that are in part derived from their molar masses and from their stereochemistry [3],[4],[5],[6]. Typically, they are strong but brittle materials with comparable mechanical properties to polystyrene that may enable them to replace petroleum based polymers in many applications including packaging, textile, electronic and biomedical among others [3]. While PLAs used for biomedical applications present a molar mass of 5 to 30 kg.mol^{-1}, those used to produce packaging materials necessitate a minimum of 35 kg.mol^{-1}. Orthopedic and other temporary implants used in bone surgery are made from polylactides with molar masses from 150.000 to 300.000 g.mol^{-1} [7]. Mechanicals properties of PLA-based materials depend principally on the inherent

crystallinity linked to the number of L-lactide units. PLLA from between 50 to 93% of L-lactic acid is strictly amorphous and presents poor mechanical properties [7]. Better mechanical properties have been obtained for PLLA containing 98% of L-lactide units. While significant steps have been made in the development of PLAs, intensive research has been directed towards making the synthesis more 'green'. One approach has been to replace toxic and polluting heavy metal catalysts such as tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) traditionally used in *L*-lactide (LLA) bulk ROP [reaching hundred of kdaltons within few minutes[8]], with organic compounds.[9],[10],[11] Such organocatalysts present lower toxicity than their organometallic counterparts and can, for the most part, be safely used in biomedical and electronic applications and be easily removed from the final PLLA material. A major challenge, however, remains before such approaches can be applied on an industrial scale, namely application of organocatalysis in bulk. Bulk polymerization requires the use of temperatures as high as 180°C - equal to the melting temperature of PLLA[5] - in order to produce perfect PLLA chains by reactive extrusion processes preferred in industry. Besides the difficulty of synthesizing perfect PLLA chains at such high temperature without any racemization, transesterification reactions and macrocyclizations (Scheme 1), which are known to lower their thermal and mechanical properties, organic catalysts suffer from low thermal stability and hence become deactivated. Overcoming this limitation presents a significant challenge and herein we bring together the efforts that have been reported to synthesize PLLAs under solvent free conditions at high temperature (in bulk). Basic, acidic and bicomponent catalyst systems which are naturally occurring, inspired or not by Nature have been studied. Note that for some clarity, natural catalysts presented in the forthcoming paragraphs are drawn in green, the Nature-inspired ones in yellow, while others will be in black.

BASIC AND NUCEOPHILIC CATALYSTS

The first reported attempts at conducting the metal-free ROP of LLA in bulk were conducted by Matsumura *et al.* using enzymes as catalysts.[12],[13] Among the several lipases tested, it was reported that *Lipase pseudomonas PS* gave the more promising results. Indeed, the enzymatic catalysis of LLA ROP in bulk at 100°C led to a high weight-average molar mass polymer (M_w= 48 kg.mol^{-1}) with low dispersity ($Đ_M$=1.2). Despite this relative success, the low polymerization temperatures applied were required in order to prevent the enzyme degradation and long polymerization times were needed up to 7 days to reach a

monomer conversion of 82%. Furthermore, low polymer yields of 10% were obtained as a consequence of the removal of the major oligomeric LLA fraction by precipitation. These significant issues were also encountered for the other lipase systems studied such as Novozym 435[14] and *candida antartica* lipase B (CAL-B)[15],[16] reducing the potential for using enzymes as catalysts for LA ROP in bulk.

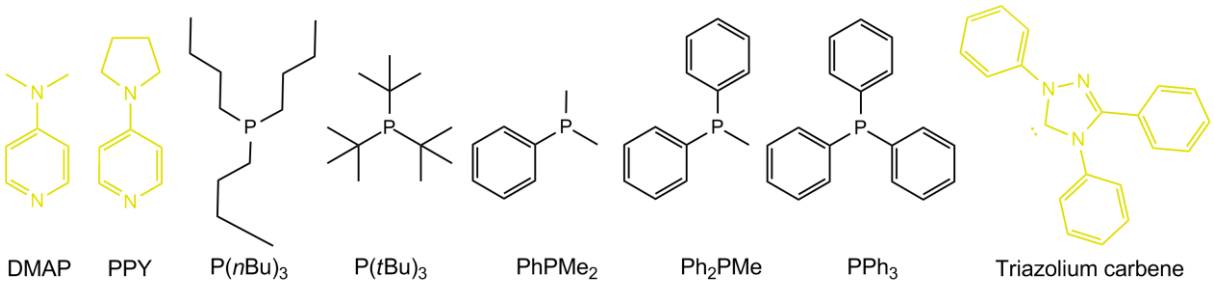

Figure 2. Basic and nucleophilic organocatalysts (part 1).

In 2001, the group of Hedrick reported the first organic compound inspired from naturally occurring pyridines, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), for the ROP of LLA (Figure 3).[17] Within this study, the authors reported the bulk polymerization of LLA at 185°C. DMAP proved to be highly active and selective for the controlled ROP of LLA in presence of benzyl alcohol (DMAP/BnOH=2/1) in less than 10 minutes. Predictable degrees of polymerization (DPs) up to 60 and narrow dispersities ($Đ_M$ < 1.2) were obtained even at 185°C. The polymerization pathway was ascribed to be an activated-monomer mechanism involving a nucleophilic attack by DMAP on the monomer to generate an alkoxyde /acyl pyridinium zwitterion. Later on, the versatility of DMAP was further demonstrated by initiating the ROP of LLA from pyrenemethanol at 140°C.[18] This catalyst, however, is highly toxic (LD_{50} in rats, intravenous: 56 mg/kg)[19] and only PLLA of molar mass lower than 10 kg.mol^{-1} could be obtained. Hedrick and coworkers also reported that 4-pyrrolidinopyridine (PPY) was a highly active catalyst for the bulk ROP of DLLA at 135 °C.[17] A subsequent study by Katiyar *et al.* investigated the efficiency of PPY for the bulk ROP of LLA at 120°C.[20] In the absence of added protic initiator, polymers with number-average molar mass (M_n) up to 18 kg.mol^{-1} were achieved. MALDI-ToF MS analysis revealed that PPY was acting as both the catalyst and initiator, however, under these conditions, this catalyst was also promoting significant transesterification side reactions. Notably, increasing the temperature in the polymerization from 120 to 160°C increased the rate of polymerization as may be expected. Nevertheless, a further loss of control was highlighted when the

polymerization was performed at 160°C as evidenced by the decrease of M_n even though the conversion increases.

Beyond the use of DMAP and PPY, other nucleophilic catalysts have been studied for the bulk ROP of LA. In 2002, the group of Hedrick reported the controlled ROP of LLA catalyzed by phosphines.[21] Reactions were conducted in bulk at 135°C or 180°C in the presence of benzyl alcohol as initiator with targeted DP between 30 and 60. A linear correlation between the DP and the monomer conversion was observed with the resultant polymers displaying a relatively low dispersity (for bulk polymerization) from 1.11 to 1.40. P(*n*-Bu)$_3$ was shown to be very active, enabling the polymerization within 10 min and phosphine activity decreases with decreasing basicity and nucleophilicity as: P(*n*-Bu)$_3$> P(*t*-Bu)$_3$> PhPMe$_2$> Ph$_2$PMe > PPh$_3$> P(MeO)$_3$ (unreactive). These results indicate that electron availability at phosphorous atom is a dominant variable, as expected in the nucleophilic catalysis mechanism. Nevertheless, phosphines are flammable (flash point = 37°C) and susceptible to undergo oxidation [22] since phosphorous has a strong oxygenophilic character and a suspected thermal stability. Indeed, the reaction media turned to an amber color after long polymerization times when the less nucleophile catalysts were used, this was especially notable at 180°C.

N-Heterocyclic carbenes (NHCs) have been widely studied as potent nucleophilic catalysts for the ROP of cyclic esters and other monomers on account of their highly reactive nature and tuneability of the catalyst structure.[10] Despite the large number of studies in this area, the only statement of using NHCs for ROP of LLA in bulk was reported by some of us in 2007.[23] Using 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene carbene and alcohol initiators at 135°C, highly isotactic PLLAs were obtained with experimental M_n which are comparable to the theoretical values up to 10 kg.mol^{-1}and narrow dispersities ($Đ_M$~1.15). Notably however, increasing the temperature of the polymerization reaction led to a loss of control that resulted from the thermal decomposition of the triazolium NHC.

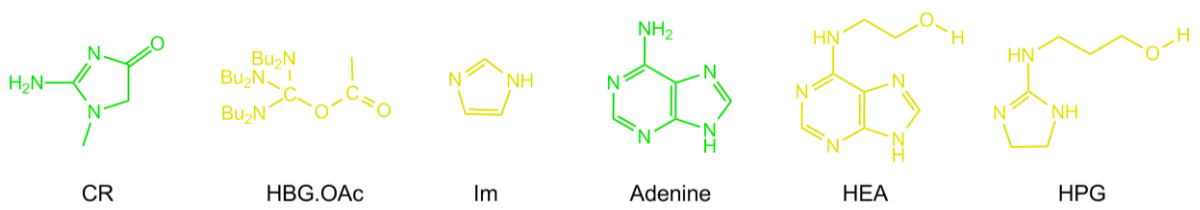

Figure 3.Basic and nucleophilic organocatalysts (part 2).

A range of other nucleophilic and basic catalysts have also been studied in the bulk ROP of LA. In 2004, the group of Zhao studied two guanidine-like organocatalysts in this

process. Creatinine (CR),[24] a naturally-sourced compound, and hexabutyl guanidinium acetate (HBG.OAc),[25] a synthetic analogue, were studied for their bulk ROP activity (Figure 4). Creatinine enabled the ROP of LLA to produce PLLA with M_n= 15.6 kg.mol^{-1} in 96 h at high temperature, 165 °C. While the controlled/living nature of the polymerization was not reported, in contrast, guanidinium acetate exhibits a highly-controlled polymerization at 110 °C to produce PLLA with DPs up to 150 and narrow dispersity (*ca*. 1.09) within 24h. Again, these organocatalysts were not able to be applied at temperatures as high as 180°C with racemization of the monomer being particularly highlighted as a significant side reaction for both catalysts. Highly active acyclic guanidines [18] were reported enabling the polymerization of LLA at 140°C. The most promising one, 1,1,3,3-tetramethyl-guanidine, achieved a monomer conversion of 45% within 30 min and led to a polymer with a M_n of 12 kg.mol^{-1}. However, the control of the polymerization is questionable since no detailed study was reported such as the relationship between M_n and the monomer conversion for example.

Imidazole (Im) and imidazole-based catalysts have also been found to be interesting for the synthesis of PLLAs. Kricheldorf reported the application of Im for the synthesis of cyclic PLLA.[26] The polymerization of LLA was conducted in the absence of protic initiator, at 100 °C with a LA-to-Im ratio of 20. The polymerization process was postulated to be a combination of a chain-growth ROP, with PLA macromolecules containing an Imidazole α-chain end, and a step-growth polymerization, *i.e.*the formation of cyclic polymers *via* a kinetically controlled end-to-end cyclisation leading to the subsequent Im elimination. Transesterification side-reactions were observed during the LLA polymerization and all synthesized PLAs were amorphous, characteristic of poly(*D*,*L*- (or *meso*) lactide) materials due to the racemization.

Adenine end-capped PLLAs were synthesized by Nogueira *et al.*[27] This natural molecule containing pyrimidine and imidazole moieties was used as both catalyst and initiator at 135°C under solvent free conditions. However, the polymerization was not controlled and led to oligomers with high dispersity ($1.48 < Đ_M < 2.05$) and non-predictable chain length (based on the monomer-to-initiator ratio). Analysis of the resultant polymers by MALDI ToF MS revealed that transesterification reactions occur. Furthermore, three major populations were identified at the beginning of the ROP (*i*) PLA initiated by adenine (*ii*) PLA containing carboxylic acid at the α-chain end due to adenine initiation followed by water replacement and also (*iii*) cyclic PLA. At higher monomer conversions and at high polymerization temperature, the proportion of PLA macrocycles increases. The presence of a significant

amount of cyclic PLAs suggests that the imidazole moiety of adenine initiates the polymerization as previously described by Kricheldorf.[26] The authors also highlighted that increasing the polymerization temperature up to 180°C leads to the degradation of the polymer, characterized by a deep brown color. In order to avoid the generation of cyclic PLAs and to reach higher M_n the group of Penczek [28] developed a hydroxyalkylated adenine, 6-(2-hydroxyethyl)-aminopurine (HEA). This strong base, which has a structure very close to that of adenine, acts as both catalyst and initiator for the ROP of LLA in bulk at 120 °C. High molar mass PLAs up to 56 kg.mol^{-1} were isolated with relatively narrow dispersity (< 1.31) within 30.5 h. No transesterification was observed and only HEA end-capped PLLAs were observed by MALDI ToF MS analysis of the resultant polymer. It was proposed that the absence of PLA macrocycles resulted from the steric hindrance near to the imidazole moiety generated by the hydroxyalkyl group. The same group also developed a hydroxyalkylated imidazole, *i.e.*3-[(4,5-dihydro-1H-imidazol-2-yl)amino]-propanol (HPG), that enabled the bulk polymerization of LLA with shorter reaction times at 120 °C.[28] However, PLLAs with lower molar masses *ca*. 13 kg.mol^{-1}and broad dispersity *ca*. 1.63 were obtained. HPG also results in initiation from both the -OH and -NH groups and hence leads to two PLA arms for each HPG molecule. For both catalysts racemization of the monomer feedstock occurred, thus limiting their applicability in bulk ROP.

ACIDIC CATALYSTS

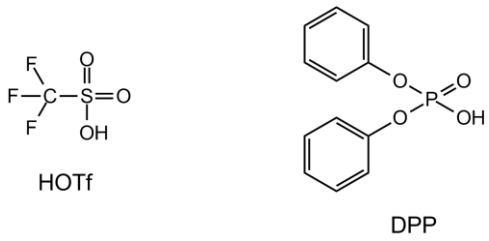

Figure 4. Acidic catalysts (part 3).

Basic organo-catalysts for the LLA ROP under solvent free conditions have been widely investigated with several principal drawbacks such as their low thermal stability, the polymer degradation at temperature as high as 180°C and the base-catalyzed racemization of LLA. These features lead mainly to a poor control of the polymerization especially when high DPs were targeted. In contrast, acids have been poorly explored with only two studies in bulk[29],[30] over the past 20 years. It is noteworthy that the only acid catalyst which has been found to be active for the ROP of LLA in solvent is trifluoromethane sulfonic acid

(HOTf).[31] This synthetic molecule has been found to be a bifunctional catalyst acting as a proton shuttle *via* its acidic hydrogen and basic oxygen atoms.[32] Bednarek *et al.*[29] tried to use this feature in combination with amine initiators for the polymerization of LLA in bulk at 120°C. However, besides the fact that secondary amines can potentially initiate two PLLA chains, only oligomers with high dispersities (between 1.87 and 3.8) resulted. Further analysis of the resultant polymer revealed a co-initiation with water had occurred, which is a significant side reaction when ROP are catalyzed by Bronsted acids. Diphenylphosphate (DPP), which also acts as a bifunctional catalyst, has been intensively studied for the ROP of lactones however was an inefficient catalyst for the ROP of LA in solvent[33].Surprisingly, Saito *et al.* [30] showed that this catalyst– 2 eq *vs* initiator for a DP = 50 – could activate the polymerization of LLA at 130°C obtaining a highly isotactic PLLA with a relatively good control over the molecular parameters of the resultant polymer within 22 h.

BICOMPONENT CATALYSTS

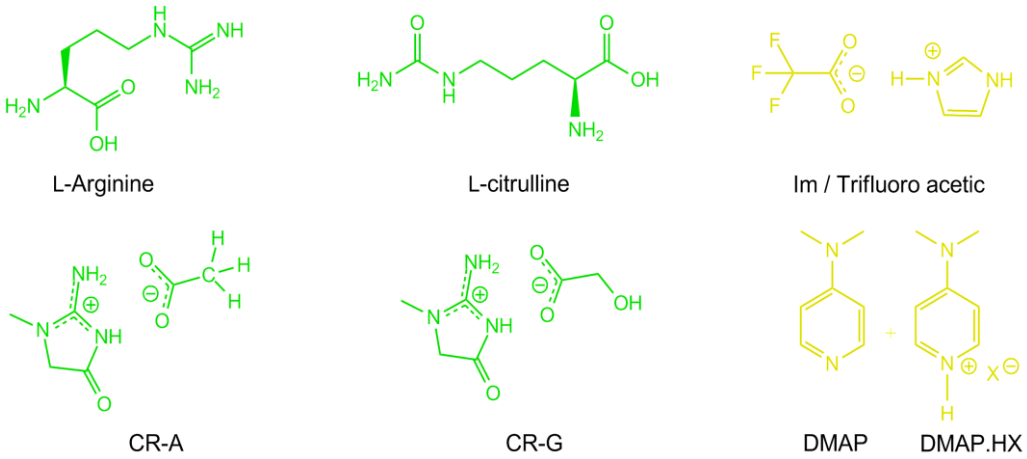

Figure 5. Bicomponent catalytic systems (part 4).

Beyond simple acids and bases, bicomponent catalytic systems have been also studied as catalysts in ROP of lactide.[34],[35],[36],[37] Some such systems could provide catalysts with significant potential for bulk polymerization of LA since the association of basic and acidic molecules leads to a salt, which increases the thermal stability of the basic compound. However, the most interesting characteristic of theses catalysts is their ability to activate both the monomer and the initiator during the course of the polymerization *via* hydrogen bonding. Creatinine combined with acetic acid (CR-A) and glycolic acid (CR-G) were first developed by the group of Zhao and studied in the bulk ROP of LLA at 130°C (for CR-A) and 110°C (for CR-G).[34] With such catalysts, racemization of LLA was significant and polymers with a mixture of α-chain end were isolated as creatinine is able to initiate ROP as well as be removed by residual water present in the system. Nevertheless, good control over the polymerization was obtained and polymers with M_n up to 15 kg.mol^{-1}were obtained within about four days.

L-Citrulline and *L*-arginine[35] were also studied as catalysts for LA ROP in bulk. These α-amino acids have the particularity of containing both acidic and basic moieties in one molecule. While analysis of polymers resulting from ROP in bulk at 160 °C revealed a good correlation between the $M_{n,th}$ and $M_{n,exp}$ up to 14 kg.mol^{-1}, the final polymers were highly transesterified. Three types of PLLAs were also noticed: two linear structures bearing either a carboxylic acid or the α-amino acids as α-chain ends and cyclic PLLAs. A bifunctional catalytic system composed of imidazole and trifluoro acetic acid in the presence of benzyl alcohol was studied by some of us.[36] The combination of the bicomponent system to the exogenous alcohol actually mimics the catalytic triad of an enzyme active in ROP and

allowed for the LLA ROP to proceed at 140°C. The high activity of this catalyst system was shown by the achievement of a 84% monomer conversion after only 3.7 h ($[LLA]_0/[Im\ salt]_0/[BnOH]_0$ = 70/5/1) with the resultant polymers being produced in a controlled manner. Despite the fact that the selectivity was quite good with a low level of transesterification process, a low molar mass population initiated by water was observed by MALDI-ToF analysis of the crude polymer. TGA analysis of the salt revealed a thermal degradation temperature of 170 °C which would limit its application under industrially-relevant bulk polymerization conditions.

In order to compensate the lack of chain-end fidelity usually observed for previously described bicomponent catalysts, Guillerm *et al.*[18] and the group of Peruch[37] reported the application of a DMAP:DMAP.HX catalytic system (2:1 mol% vs monomer) in the presence of protic initiators at 100 °C. The most exciting feature of this system is the high activity for ROP with PLLAs of *ca.* 14 $kg.mol^{-1}$ being synthesized within only 1 h using DMAP:DMAP.HOTf.[37] The absence of transesterification reactions during the course of the polymerization up to 90% monomer conversion and the very narrow dispersities indicated that the high activity is combined with a high selectivity. However, base-catalyzed racemization still occurs with a PLLA melting temperature of only 130°C.

SUMMARY AND PERSPECTIVE

It is clear that compounds of Mother Nature have been a relevant source of inspiration over the past 20 years for the catalysis of LLA ROP under solvent free conditions. Low cost Brønsted bases have been widely used and lead to moderate-to-good control over ROP. DMAP and its salts appear as the most interesting catalysts; however, the catalysis of deleterious side reactions such as transesterification and racemization, as well as poor thermal stability of the catalysts and polymer degradation at temperatures as high as 180 °C leading to brown coloration of the polymers will prevent their further development. Acidic compounds which are more thermally stable and are in many cases thermally activated catalysts for ROP have received much less attention. Diphenylphosphate has been shown to lead to highly isotactic PLLAs and offers very promising perspectives for acidic catalysts however, the current low activity and hence long reaction times for ROP are a limitation towards their wider application in an industrial-scale process. Bicomponent catalytic systems appear to also present significant promise with the salt formation leading to more thermally-stable catalysts

however, to date the combination of high thermal stability with high reactivity has not been fully realized and remains an unsolved challenge in LA ROP.

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